SYNOPSIS

Efficient synthesis and biological activity evaluation of some fused pyrimidopyrimidine ,pyrimidothiazine and pyrimidooxazine derivatives.

SHORT RESUME OF THE PLAN PROPOSED FOR INVESTIGATION FOR Ph.D DEGREE UNDER THE FACULTY OF SCIENCE

To be submitted to

SWAMI RAMANAND TEERTH MARATHWADA UNIVERSITY, NANDED

By

Mr. N. B. Chavhan

(Research Scholar)

Yeshwant College Nanded

Under the Guidance of

Dr. S.B. Sirsat

(Research Guide)

Assistant Professor

P.G. Department of Chemistry

Yeshwant College Nanded.

June - 2019

Efficient synthesis and biological activity evaluation of some fused pyrimidopyrimidine ,pyrimidothiazine and pyrimidooxazine derivatives.

Pyrimidine is a class of aromatic heterocycle containing two nitrogen atoms at positions 1 and 3 of the six-membered ring which shows wide range of remarkable pharmacological activities. Condensed pyrimidine that is pyrimido pyrimidine derivatives have been reported as anti-microbial, analgesic, anti-viral, antiinflammatory, anti- HIV, anti-tubercular, anti-tumor, anti-neoplastic, anti-malaria, diuretic, cardiovascular agents and hypnotic drugs for the nervous system etc.

Amongst all heterocyclic compounds, pyrimidine exhibits broad spectrum of biological activities as of its occurrence in deoxyribonucleic acid (DNA) bases cytosine, thymine, and uracil. The pyrimidine skeleton also present in vitamin B1 and barbiturates.

Thiazine is a six membered hetrocycle containing nitrogen and sulphur in the ring has led to unabated research in their synthetic methodologies.

Thiazine contains two hetero atoms such as nitrogen and sulphur placed at 1,3-positions. Thiazines are very useful units in the field of medicinal chemistry and have been reported to exhibit a variety of biological activates such as antimicrobial antiviral , antifungal, blood platelet aggregation inhibitors, antihistaminic, antioxidant ,. Moreover, thiazine derivatives act as effective corrosion inhibitor.

Oxazines are heterocyclic compounds containing one oxygen and one nitrogen in six membered ring . Many isomers of oxazine are exist exist depending on the relative position of the heteroatoms and relative position of the double bonds but 1,3-Oxazines attract more attention as they constitute an important class of both natural and non-natural products.

Heterocycles containing the oxazine nucleus were found to possess a wide range of valuable biological properties like analgesic, anti-inflammatory, anti-leukemic, antimalarial1-3, antipyretic, anticonvulsant and antimicrobial activities4-8. Benzo-1,3-oxazines are also known to be biologically active, demonstrating anti-rheumatic, antianginal,

In continuation of our work. In this thesis our paln is to synthesize pyrimido pyrimidine , pyrimido thiazine and pyrimidooxazine containing more reactive functional groups for further cyclisation and derivatization using ecofriendly solvents. The synthesized compounds reacting with various nucleophiles such as substituted aromatic amines , aromatic phenol, various active methylene compounds and alicyclic heterocyclic compounds to construct derivatives of pyrimido pyrimidine , pyrimido thiazine and pyrimidooxazine and these synthesized compounds are screened for biological activities .

Literature Survey :

Bruno et,al reported the synthesis of some new 2,5-cycloamino-5H –benzopyrano[4,3d]pyrimidines and screened them for antiinflammatory, analgesic and antipyretic activities and in vitro antiplatelet activity. All the compounds failed to exhibit antiinflammatory, analgesic and antipyretic activities but they showed an interesting antiplatelet activity .

Sunil Dhanya, et al in 2013 ,a new series of 1,3oxazines have been synthesized from acid-catalyzed reaction between chalcones and urea. Excellent antibacterial activity was exhibited by oxazine against gram +ve bacteria. And these compounds were found to be highly sensitive against gram –ve bacteria. And some oxazine derivatives show excellent antifungal activity.

Kadhim reported a novel azachalcone compound that was prepared through the reaction of acetylated pyridine with 4-hydroxybenzaldehyde Later the azachalcone was treated with thiourea to give a high yield of the thiazine

derivative ((E)-3-(4-hydroxyphenyl)-1-(pyridin-3-yl) prop-2-en-1one). The synthesized compound was characterized by infrared, ultra-violet, 1H-NMR spectroscopy and elemental analysis. The obtained compound were tested for anti-bacterial and antifungal properties and showed good activities.

Kategaonkar et al, reported ionic liquid catalyzed multicomponent synthesis of 3,4-dihydro-3substituted-2H-naphtho[2,1-e][1,3]oxazine derivatives from 1-naphthol, various anilines and formalin at room temperature stirring. The sixmembered N,O- heterocyclic skeleton was constructed via 1-benzyl-3-methyl imidazolium hydrogen sulphate [bnmim] [HSO4] promoted Mannich type reaction .

Hitchings et,al, made an important observation that a large number of 2, 4-diamino pyrimidines and some 2- amino- 4 hydroxypyrimidines are antagonists of folic acid.

Futterman S. et,al eventually proved that these pyrimidines were inhibitors of the enzyme dihydrofolatereductase (DHFR).

Cheng CC et,al showed that 2, 4-diaminopyrimidine drugs, pyrimethamine is a selective inhibitor of the DHFR of malarial plasmodia and trimethoprim, an antibacterial drug is also a selective inhibitor and selectively inhibits bacterial DHFR.

Objectives :

Specific objectives of our current research program include the synthesis of novel pyrimidopyrimidine ,pyrimido thiazine and pyrimidooxazine and their derivatives.

- One pot synthesis of amino pyrimidine and amino thiazine and amino oxazine using chalcone and guanidine nitrate , thiourea and urea.
- Reaction of amino pyrimidine and amino thiazine and amino oxazine nucleus with Michael accepter to give pyrimido pyrimidine , pyrimido thiazine and pyrimidooxazine.

- Reaction of pyrimidopyrimidine ,pyrimido thiazine and pyrimidooxazine nucleus with various aromatic phenols.
- Reaction of pyrimidopyrimidine ,pyrimido thiazine and pyrimidooxazine nucleus with various aromatic amines.
- Reaction of pyrimidopyrimidine ,pyrimido thiazine and pyrimidooxazine nucleus with various hetryl amines.
- Reaction of pyrimidopyrimidine ,pyrimido thiazine and pyrimidooxazine nucleus with various different hydrazines.
- Pharmacological activity of above synthesized compounds.

Methodology:

By known synthetic method synthesis of amino pyrimidine , amino thiazine and amino oxazine .

The synthesized amino pyrimidine , amino thiazine and amino oxazine is act as a Michael donars and it condence with Michael acceptar to give pyrimido pyrimidine,pyrimido thiazine and pyrimidooxazine .

Pyrimidopyrimidine ,pyrimido thiazine and pyrimidooxazine act as a electrophillic species condence with various nucleophile such as aromatic amines, aromatic phenols, hetryl amines and also cyclise with some different hydrazine and biological evaluation of above synthesized compounds.

International status:

Since from the last three decades, we have witnessed the revolutionary synthesis pyrimido pyrimidine,pyrimido thiazine and pyrimidooxazine of many researchers throughout the world. Although there are huge number of articles on pyrimidopyrimidine ,pyrimido thiazine and pyrimidooxazine.

1. Cenicola and Co-workers evaluated some imidazolopyrimidines for antiinflammatory, analgesic and antipyretic activities. Anti-inflammatory

activity was studied by carrageenan- induced paw oedema in rats and found to show activity comparable to indomethacin.

2. FumiyoshiIshikawa, and Co-workers synthesized cyclic Guanidines derivatives and then screened them for blood platelet aggregation inhibitors activity.
3. FarhatJubeen and co-workers gives review on Eco-friendly synthesis of pyrimidines and its derivatives.
4. Ahmed Hamza and Co-workers synthesized Some New Triazine, 1, 3-Oxazine, Fused Pyridine and Pyrimidine Derivatives with their antibacterial activity.
5. Eleni A. R and Co-Workers was synthesized an amine and amide derivatives having 2, 6-di-tert-butyl phenol moiety, all most all are anti-oxidants and it reduces acute inflammation and inhibit COX-1 and lipoxygenase activity. 2, 6-di-tert-butyl 1, 4-thiomorpholine-4-yl methyl phenol is having most potent anti-inflammatory activity.
6. ZainabAmer and Co-workers: synthesized some thiazine and pyrazole derivatives by using chalcones. In this study, chalcones were synthesised by condensing 2acetylpyridine with aromatic aldehyde derivatives in dilute ethanolic potassium hydroxide solution at room temperature. Thiazine and Pyrazole were synthesized by reaction between chalcones with thiourea and urea respectively.
7. FarhadHatamjafari and Co-workers give Synthesis of 1,2-Dihydro-1 arylnaphtho [1,2-e] [1,3] oxazine-3-ones using nano-Fe2O3 as an acid catalyst and solvent-free conditions .

National Status :

Apart from the international contribution some of the Indian researchers have also made their mark on synthesis of pyrimido pyrimidine , pyrimido thiazine and pyrimidooxazine.

1. Sunil Dhanya,et al in 2013, gives a new series of 4-(4-substituitedphenyl)-6-substituited-6H-1,3oxazines using chalcones and urea in acidic medium. And these compounds exhibit excellent antibacterial activity .

2. Ramesh L. Sawant et al in 2012 A new series of Schiff bases of 1, 3-oxazines were synthesized in three steps. In the first step, 4bromoacetophenone and substituted aromatic aldehyde reacted in the presence of sodium hydroxide to give substituted chalcones (ClaisenSchmidt condensation). In second step, substituted chalcones reacted with urea to produce 4-(4bromophenyl)-6-(substituted phenyl)-6H-1,3-oxazin-2-amine analogues. In third step, these compounds were reacted withsubstituted aromatic aldehydes to produce 4-(4-bromophenyl)6(substituted phenyl)- 2-{[(1E) (substituted phenyl) methylidenene]}-6H-1,3-oxazin-amine. The newly synthesized compounds were characterized by IR, NMR and screened for their antimicrobial activity and antifungal activity .
3. Ram S G et al; (2013) synthesized 1, 3 thiazines by refluxing the mixture of 2-Hydroxy-3-bromo/nitro -5-chlorochalcone and phenyl thiourea in alcohol and aq.KOH. It was screened against anti-bacterial and anti-fungal activity.
4. Varalakshmi et al; (2011) synthesized a series of novel chalcones from different benzaldehydes with various Acetophenones .The resulted chalcones were treated with thiourea leading to the formation of corresponding thiazines in good yields. The compounds were screened for the antibacterial activity.
5. FarooqueHaiderZulfequarHaider (2012): Synthesise some 1,3 -thiazines in two series, first series starting material is 2- hydroxyacetophenone and Second series starting material is 2hydroxy- 5- methyl acetophenone .
6. Bahekar et, alreported the synthesis of some [2-amino-6-(4-substituted aryl)-4-(4substituted phenyl)-1,6-dihydropyrimidin-5yl]acetic acid derivatives and evaluated for anti-inflammatory activity. Only few of them showed remarkable anti-inflammatory activity.
7. Mishra et.al. synthesized various derivatives of pyrimidines. The fungicidal activities of the compound were evaluated against P. infestans and C. falcatum by the usual agar plate technique at 1000, 100 and 10 ppm concentration.

Regional status :

1. Sambhaji P. vartale, Vijay N.Bhosale ,Sandeep V. Khansole and ramdas N. Katapalle (2009) . A convenient one pot synthesis of 3-cyno-9-methyl-2-methylthio-4-oxo-4H-pyrimidi-[2,1-b][4,5-b]quinoline and its reaction with selected nucleophiles. Letters in organic chemistry Vol.6,No7,544-548.
2. ReshalDeshmukh give Synthesis, structural study and biological evaluation of 1,3-thiazine.
3. A.H. Kategaonkaret,al give Microwave assisted synthesis of pyrimido[4,5d]pyrimidine derivatives in dry media .
4. Baheti KG, Jadhav JS, Suryawanshi AT and Kuberkar SV (2005) Novel synthesis and antibacterial activity of 15-iminobenzothiazole[2,3b] pyrimido [5,6e] pyrimido[2,3]benzothiazole-14-H ones and its 3,10 disubstituted derivatives. Ind J Chem 44B: 834D
5. Pingle MS, Vartale SP, Bhosale VN and Kuberkar SV (2006) A convenient synthesis of 3-cyano-4-imino-2- methylthio-*4H*pyrimido [2,1-*b*] [1,3] benzothiazole and its reactions with selected nucleophilesArkivoc X, 190D.

Scope of the study :

Lot of research work is going on all over the world to investigate organic compounds which will act as effective medicines as anti-HIV, anti-Cancer and anti-tuberculsotatic drug Antibacterial. National Institutes of Health, National Cancer Institute, Bethesda, Maryland, USA showed keen interest in evaluation of such compounds. It is surmised that some newly synthesized compounds mentioned in our proposal using green solventsand these synthesized compounds would exhibit properties required for effective drugs. Synthesis and screening of newly synthesized compounds would lead to the formation of pharmacological importance.

Proposed work plan with tentative chapter scheme .

Year	Quarters (Periods of three months)	Milestones
Year I	1 st Quarter	Reference Work
	2nd Quarter	Topic first literature survey
	3rd Quarter	Topic second Experimental Work and characterization
	4th Quarter	Topic second Experimental Work and characterization
Year II	1 st Quarter	Topic third Experimental Work and
	2nd Quarter	Topic third Experimental Work and characterization
	3rd Quarter	Topic Fourth Experimental Work and characterization
	4th Quarter	Topic Fourth Experimental Work and characterization
Year III	1 st Quarter	Topic Fifth Experimental Work and characterization
	2nd Quarter	Topic sixth Biological evaluation
	3rd Quarter	Topic sixth Biological evaluation
	4th Quarter	Writing and typing of the research work and submission of the research work

Expected Outcome :

It is planned to synthesis fused heterocycles using unconventional solvents i.e. bio degradable solvents in good yields and synthesized compounds are expected to show good biological activity.

Referance :

- Beena K et al .Design, synthesis, characterization and evaluation of some 1,3-oxazine derivatives as potent antimicrobial agents 2013: 5 (4):257-260.
- Mohana, K.N., B.N.P. Kumar and L. Mallesha, 2013. Synthesis and biological activity of some pyrimidinederivatives. Drug Invention Today, 5(3): 216-222.
- Simerpreet and C.S Damanjit, *Pharmacophore.* 4(3), 70-88 (2013).
- Sindhu T J *et al*. International Journal of Pharma Sciences and Research (IJPSR).
- FarhadHatamjafari*et al*.A Facile One-Pot Solvent-Free Synthesis of 1,2-Dihydro-1 arylnaphtho [1,2-e] [1,3] oxazine-3-ones 2014.
- Wang, W.; Zhao, B.; Xu, C.; Wu, W. Synthesis and Antitumor Activity of the Thiazoline and Thiazine Multithioether. Int. J. Org. Chem. 2012, 2012, 117–120Preet, S.; Damanjit., C.S. Synthesis and biological evaluation of 1,3-thiazines—A review. Pharmacophore2013,4, 70–88.
- Rai, V.K.; Rai, P.; Thakur, Y. Masked mercapto acid-driven MCR in task-specific ionic liquid: A new
  sterocontrolled entry into bicyclic 1,3-thiazines. Tetrahedron Lett.2013, 54, 6469–6473.
- Charris, J.; Barazarte, A.; Domínguez, J.; Gamboa, N. Microwave-assisted synthesis of quinolones and 4H-1,4-benzo-thiazine 1,1-dioxides. J. Chem. Res. 2005, 2005, 27–28.

- Simerpreet and Cannoosingh D. Synthesis and biological evaluation of 1,3 thiazine -A review. Pharmacophore (An International Research Journal). 2013;4(3):70-88.
- Boulton A J, McKillop A, Comprehensive HteterocyclicChem, 1984; 3: 1038.
- Sundari V, Nagarjan G, Valliappan R, Synthesis and biological activities of some N- hydroxymethylene and N-methoxymethylenethiazines, Med. Chem. Res, 2007; 16: 402-407.
- Hemapriya V, Parmeswari K, Bharthy G, The inhibition effect of thiazine compounds towards the corrosion of mild steel in sulphuric acid media, Rasayan J. Chem, 2012;5: 468-476.
- M. Lebrini, M. Lagrenee, M. Traisnel, L. Gengembre, H. Vezin, F. Bentiss, *Appl. Surf. Sci*. 253 (2007) 9267.
- T. H. Brown, R. C. Blakemore, G. J. Durant, J. C. Emmett, C. R. Ganeline and M. E. Parsons, D. A. Rawlings and T. F. Walker, Isocytosine H2-receptor histamine – antagonists part I. Oxmetidine and related compounds, *Eur. J. Med. Chem*. 23 (1988) 53–62.
- Rathore BS, Kumar M. Synthesis of 7-chloro-5- trifluoromethyl/7-fluoro/7-trifluoromethyl-4H-1,4- benzothiazines as antimicrobial agents. Bioorg Med Chem 2006;14:5678-82.
- Vishenkova, D. A.; Korotkova, E. I.; Dorozhko, E. V.; Derina, K. V. *Procedia Chem.* 2014, *10*, 519..
- Elrazaz, E. Z.; A, K. A. M.; Serya, Rabah A. T.; Ismail, N. S. M.; Abou El Ella, D. A. *Future J.Pharm. Sci.* 2016, *1*, 33.
- Luo, Y.; Deng, Y.-Q.; Wang, J.; Long, Z.-J.; Tu, Z.-C.; Peng, W.; Zhang, J.-Q.; Liu, Q.; Lu, G. *Eur. J. Med. Chem.* 2014, *78*, 65.
- Antre, R. V.; Cendilkumar, A.; Goli, D.; Andhale, G. S.; Oswal, R. J. *Saudi Pharm. J.* 2011, *19*, 233.

- Rani, P.; Kumar, N.; Sharma, P.; Kishore, D. *Int. J. Chem. Pharm. Sci.* 2013, *4*, 7.
- Osama Mohamed Ahmed; Ahmed M Hussein, *Sci Pharm*., 2011**,** 79(3), 429–447.

Mr. N. B. Chavhan

(Research Scholar)

Yeshwant College Nanded

Dr. S.B. Sirsat

(Research Guide)

Assistant Professor

P.G. Department of Chemistry

Yeshwant College Nanded